Remarks

Claims 50-65 are pending in the subject application. Applicants gratefully acknowledge the Examiner's withdrawal of the rejection under 35 U.S.C. § 101 on the grounds that the claimed invention is directed to non-statutory subject matter. Accordingly, claims 50-65 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Claims 50-65 are rejected under 35 U.S.C. § 101 on the grounds that the invention is not supported by a specific asserted utility or a well-established utility. In addition, claims 50-65 are rejected under 35 U.S.C. § 112, first paragraph, on the grounds that one skilled in the art would not know how to use the claimed invention because it is not supported by a specific or well-established utility. The Office Action of June 16, 2004 has maintained the rejection of record on the basis that the association of different isoforms of the PG1 polypeptide with tumorigenic or non-tumorigenic tissue is insufficient to provide a "real world" utility for the claimed antibodies and methods and that the as-filed specification has failed to provide a utility that is well known, immediately apparent, or implied from the specification. Applicants respectfully traverse.

Applicants respectfully submit that the as-filed specification provides a various specific teachings related to utilities associated with antibodies and splice variants (isoforms) of the PG1 polypeptide. For example, the original claims 24 and 27 of United States Patent Application Publication No. US-2002-0165345-A1 recite methods of categorizing the risk of prostate cancer in an individual comprising the step of assaying a sample taken from the individual to determine whether the individual carries an allelic variant of PG1 associated with an increased risk of prostate cancer, wherein said sample binds an antibody that binds specifically to a PG1 isoform associated with prostate cancer. Additionally, the specification at page 9, lines 24-26, teaches determining whether the PG1 protein in the sample binds an antibody specific for a PG1 isoform associated with prostate cancer and the specification, at page 97 (lines 7-15) discusses antibodies that can be generated which are capable of specifically binding to a given isoform of the PG1 protein (*e.g.*, an isoform associated with normal tissue or tumorigenic tissue). Such antibodies can be used in diagnostic assays in which protein samples from an individual are evaluated for the presence of an isoform of the PG1 protein which is found in cancerous tissue or another detectable phenotype using techniques such as Western blotting or ELISA assays.

As set forth in the specification at page 60, lines 10-15, splice junctions 3-7 and 5-8 (isoforms of PG1) were detected in tumor samples that were not previously detected in normal samples. Additionally, some exon junctions were observed in all normal samples, but were absent in tumor samples (specification at page 60, lines 22-25). Thus, it is respectfully submitted that the as-filed specification provides a utility that is well known, immediately apparent, and implied from the specification; namely, the specification teaches the use of isoforms to distinguish between diseased and normal tissues on the basis of PG1 isoforms identified by the claimed assay, particularly with respect to claims 63-65 which are directed to the detection or quantification of isoforms of the PG1 polypeptide.

Turning to the issue raised in the Office Action with respect to other protein isoforms, it is respectfully submitted that these arguments were presented to substantiate that those skilled in the art would have recognized that isoforms or particular polypeptides can be associated with various malignancies. Further to this point, Applicants respectfully submit the following additional references.

Murphy and Dotzlaw (*Molecular Endocrinology*, 1989, 3:687 (attached)) studied breast cancer and breast cancer resistance to tamoxifen therapy. The anti-tumor activity of tamoxifen involves direct competition with estrogen for binding to the estrogen receptor (ER). Murphy and Dotzlaw investigated the possibility that abnormal mRNA species for ER are present in some human breast cancer biopsies (page 688 left column, first paragraph) and are responsible for tamoxifen resistance. Murphy and Dotzlaw showed that some tumors contained the normal 6.5 kb ER mRNA and in addition smaller sized ER mRNA of about 3.8 and 2.4 kb (page 687 left column, second paragraph, and Fig. 1A). Murphy and Dotzlaw suggest that these smaller sized ER mRNA are alternatively spliced transcripts (page 691 right column, second paragraph). In some cases the abundance of the variant ER mRNAs was equal to or greater than the normal ER mRNA (page 691 right column, first paragraph). Murphy and Dotzlaw mention the possibility that variant protein products might seriously compete with the normal protein (page 691 right column first paragraph). In the discussion, the authors indicate altered forms of the steroid receptor may be associated with resistant phenotypes and altered forms of glucocorticoid receptors have been found associated with glucocorticoid resistance in mouse lymphoma cell lines (pages 689 right column, second paragraph).

Zhu *et al.* (*Int. J. Cancer*, 1997, 72:574 (attached)) explored variants of androgen receptor (AR) in normal and tumor cell lines, and identified a specific mRNA variant in some breast cancer. The variants identified in Zhu *et al.* lack the second zinc-finger domain and are expected to be unable to, or have a reduced ability to, bind to androgen response elements and activate transcription is tissue (page 574 left column, paragraph 1).

Also attached, is the work of Moolenaar *et al.* (*Int. J. Cancer*, 1992, 51:238) regarding expression of neural cell adhesion molecule (NCAM) in small cell lung tumors (SCLC). Multiple NCAM protein isoforms are expressed from a single gene by alternative splicing in normal cells. Moolenaar *et al.* hypothesized that the metastatic potential of SCLA is at least in part due to altered binding properties of NCAM as a result of, for example, alternative splicing (page 238 left column, first paragraph). Moolenaar *et al.* hypothesizes that various NCAM isoforms differ not only in their polypeptide composition but also in their biological properties (page 238 right last sentence of first paragraph). Moolenaar *et al.* also indicate that more NCAM transcripts are present in SCLC as compared to normal cells and that the increase in transcripts probably occurs by additional alternative splicing (page 242 left column, second paragraph). Moolenaar *et al.* conclude that alternative splicing contributes to NCAM protein diversity found in tumors (page 243 right last paragraph). In view of the foregoing arguments and amendments to the claims, reconsideration and withdrawal of the utility and enablement rejections is respectfully requested.

Claims 50-61 and 63-65 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. The Office Action argues that the as-filed specification fails to provide an adequate written description of the claimed invention, arguing that the disclosure of the various isoforms identified in the specification and figures are insufficient to enable the breadth of the claimed invention. Applicants respectfully traverse.

The as-filed specification, figures, and sequence listing discuss any number of polypeptides that fall within the scope of the claimed invention. As previously discussed, numerous cDNA encoding various splice variants (isoforms) of the PG1 polypeptide are disclosed in the specification and sequence listing (see, for example, specification, pages 62-64 (SEQ ID NOs: 3, 69, 100-125,

179 and 182-184). The specification and sequence listing also disclose a variety of polypeptides that are encoded by these cDNA isoforms (see, for example, specification at pages 96-97) as well as methods of making such polypeptides; additionally, peptide sequences comprising at least 8 contiguous amino acids encoded over a naturally occurring splice junction site are also taught in the specification (see, for example, pages 76 and 96 of the specification). Applicants further submit that a variety of isoforms of the claimed polypeptides are taught in the specification at Figures 14-15 and Applicants respectfully point out that claims 63-65 are directed to the detection or quantification of isoforms of the PG1 polypeptide (*e.g.*, isoforms such as those identified in Figure 15) and that adequate written description of these full length polypeptides has been provided by the as-filed specification (for example, via the sequence listing, figures, and above cited sections of the specification). Thus, it is respectfully submitted that Applicants have taught, disclosed, and provided adequate written description for a number of species of polypeptides within the scope of the instant invention and respectfully submit that the written description aspect of 35 U.S.C. § 112, first paragraph has been met by the application as filed.

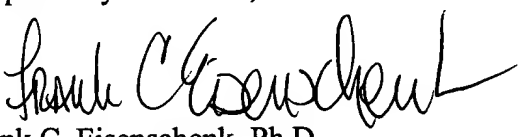
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

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Attachments: Murphy and Dotzlaw; Zhu *et al.*; and Moolenaar *et al.*